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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-028052- -00001-0000

Fecha: 2008-06-12 16:39:21 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

8 folios

Trámite : 011
Evento : 378
Actuación : 538

Referencia	:	Expediente No. 07.028.052
Asunto	:	Solicitud de Patente para **DERIVADOS DE 2-ACILAMINOTIAZOL**
Solicitante	:	**H. LUNDBECK A/S**
Clase	:	A61K 031/002, A61P 025/002
Publicada en	:	La Gaceta No. **583** Del 18 de diciembre de 2007
Fecha de Solicitud	:	21 de marzo de 2007

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de $420.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44372 de 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

COLO-03003-841-063-2
ASG\NNJ\ID-128064\WPCL3003
No. M-2008-128064\ASG

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NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 46.060
FECHA : JUNIO 9 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
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***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	420.000.00
			TOTAL : $	420.000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Rdo 03003-891-063-2

151

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-28052

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **14 DE MARZO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ____X____

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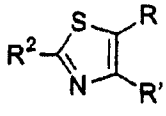
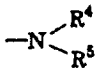
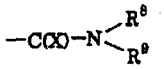
(54) Title: THIAZOLE DERIVATIVE AND PHARMACEUTICAL USE THEREOF



(I)



(i)



(ii)

(57) Abstract: A thiazole derivative of the formula (I):wherein R is a 1-optionally substituted-6-oxo-1,6-dihydro-3-pyridazinyl, R' is an optionally substituted phenyl, and R^2 is hydrogen, a group of the formula (i): wherein R^4 is hydrogen, lower alkyl or lower alkenyl, and R^5 is hydrogen, optionally substituted lower alkyl, acyl, cyclo(lower)alkyl, lower alkenyl, optionally substituted aryl or heterocyclic, or a group of the formula (ii): wherein X is oxygen or sulfur, R^8 is hydrogen or lower alkyl, R^9 is hydrogen, optionally substituted lower alkyl, cyclo(lower)alkyl, lower alkoxy or mono- or di-lower alkylamino or R^8 and R^9 may combine together to form optionally substituted saturated N-containing heterocyclic, or a salt thereof.

WO 03/039451 A2

DESCRIPTION

THIAZOLE DERIVATIVE AND PHARMACEUTICAL USE THEREOF

TECHNICAL FIELD

The present invention relates to a novel thiazole derivative which are useful as medicaments, a process for preparing an intermediate 2-alkyl-6-hydroxy-3(2H)-pyridazinone for their production and a pharmaceutical composition containing the same.

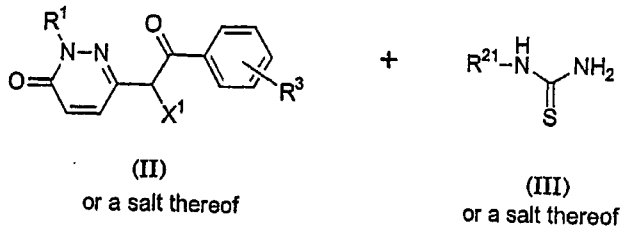
BACKGROUND ART

Adenosine is a ubiquitous biochemical messenger. Adenosine binds to and activates seven-transmembrane spanning G-protein coupled receptors, eliciting a variety of physiological responses. Adenosine receptors are divided into four known subtypes (i. e., A_1, A_{2a}, A_{2b}, and A_3). These receptor subtypes mediate different, and sometimes opposing, effects. Activation of the adenosine A_1 receptor, for example, elicits an increase in renal vascular resistance, while activation of the adenosine A_{2a} receptor elicits a decrease in renal vascular resistance. Accordingly, adenosine antagonists are useful in the prevention and/or treatment of numerous diseases, including cardiac and circulatory disorders, degenerative disorders of the central nervous system, respiratory disorders, and many diseases for which diuretic treatment is suitable.

Some 4-aryl-5-(pyridin-4-yl)thiazole derivatives having adenosine A_3 or A_{2b} inhibitory activities are known (e.g. WO-9964418A, JP-2001-114779A, etc.). However, 4-aryl-5-(6-oxo-1,6-dihydro-pyridazin-3-yl)thiazole derivatives are not known, so far. In addition, any thiazole derivatives having both of adenosine A_1 and A_{2a} inhibitory activities are not known.

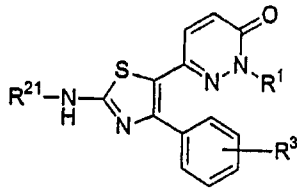
It is known that it is generally difficult to selectively alkylate 3,6-dihydroxypyridazine to give 2-alkyl-6-hydroxy- 3(2H)-pyridazinone (see "Pyridazine" ed. by R. N. Castle, John Wiley & Sons, 1973). For example, 3,6-dihydroxypyridazine is methylated with dimethyl sulfate to give 2-methyl-6-hydroxy- 3(2H)-pyridazinone derivative,

Process 1



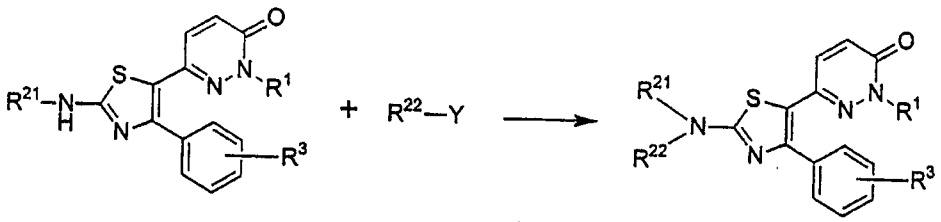
(II)
or a salt thereof

(III)
or a salt thereof



(I-1a)
or a salt thereof

Process 2

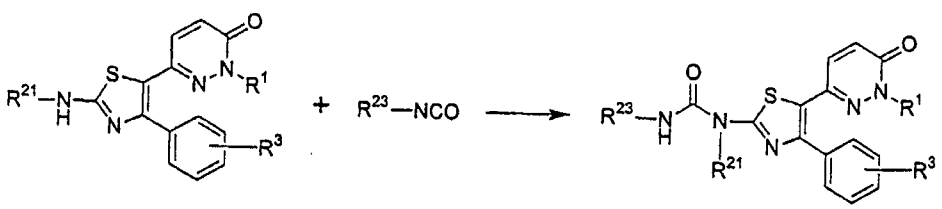


(I-1a)
or a salt thereof

(IV)

(I-1b)
or a salt thereof

Process 3

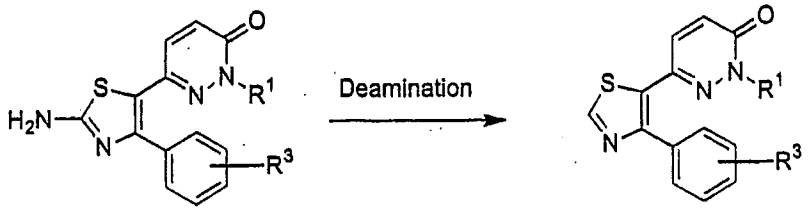


(I-1a)
or a salt thereof

(V)
or a salt thereof

(I-1c)
or a salt thereof

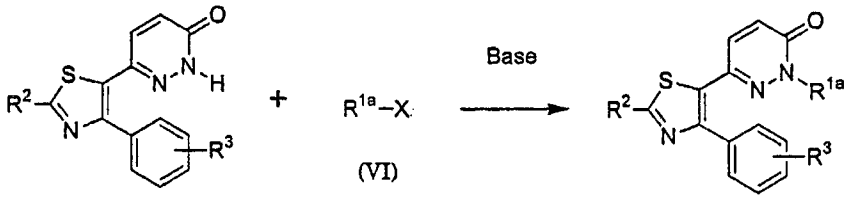
Process 4



(I-1d)
or a salt thereof

(I-1e)
or a salt thereof

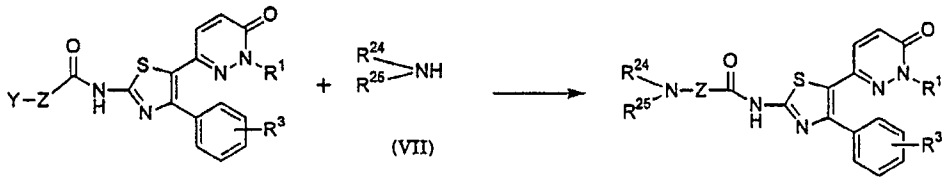
Process 5



(I-1f)
or a salt thereof

(I-1g)
or a salt thereof

Process 6



(I-1h)
or a salt thereof

(I-1j)
or a salt thereof

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)–4- phenyl-1,3-thiazol-2-yl]-2-(4-methoxy-phenyl)acetamide (Example 9)

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4- phenyl-1,3-thiazol-2-yl]-N'-(3-methylphenyl)urea (Example 10)

2-Isopropyl-6-[2-(methylamino)-4-phenyl-1,3-thiazol- 5-yl]-3(2H)-pyridazinone (Example 15)

[III] Test result

Table 1

Test compound (Example No.)	Adenosine receptor binding (Ki: nM)	
	A_1	A_{2a}
3	0.27	1.46
9	0.28	1.22
10	0.38	3.08
15	0.12	1.63
78	0.45	1.23
100	0.61	1.22
214	1.14	1.52
233	1.03	1.14

Test 2 : Anticatalepsy activity in Mouse

[I] Test method

The test compound (3.2mg/kg) was administered orally with ddY mice(n=7). Then, haloperidol (0.32mg/kg) was injected intraperitoneally 30 min. after the administration of the compound. Thirty minutes after the injection, the cataleptic responses of mice were measured. The forelimbs of each mouse were placed on a 3 cm high, 3 mm wide horizontal bar, and the duration of cataleptic posture was measured for up to 30 sec.

[II] Test compound

N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4- phenyl-1,3-